

Physiological Significance of ECL-Cell Histamine

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In the oxyntic mucosa of the mammalian stomach, histamine is stored in ECL cells and in mucosal mast cells. In the rat, at least 80 percent of oxyntic mucosal histamine resides in the ECL cells. Histamine is a key factor in the regulation of gastric acid secretion. Following depletion of ECL-cell histamine by treatment with α -fluoromethylhistidine (α -FMH), basal acid secretion was reduced, and gastrin-stimulated acid secretion was abolished. Vagally-induced acid secretion (by insulin injection or pylorus ligation) was unaffected by α -FMH treatment but inhibited by an H₂ antagonist. These results suggest that gastrin stimulates acid secretion via release of ECL-cell histamine, whereas vagally-induced acid secretion—although histamine-dependent—does not rely on ECL-cell histamine. Gastrin is known to have a trophic effect on the oxyntic mucosa. By combining long-term hypergastrinemia with continuous infusion of α -FMH, we were able to show that gastrin-evoked trophic effects in the stomach do not depend on ECL-cell histamine.

INTRODUCTION

In the oxyntic mucosa, between one and two percent of the cells are endocrine [1-4]. In the rat, approximately 65 percent of the endocrine cells are ECL cells, 10 percent are somatostatin (D) cells, 25 percent are A-like cells and a few are D₁/P cells [3, 5]. They are all “closed” in that they do not have direct contact with the gland lumen. The peptide hormone of the ECL cell has not yet been identified. However, it has been suggested that they secrete a calciotropic/osteotrophic hormone [6, 7].

Besides the peptide hormone, the ECL cells are known to produce and store histamine [8, 9]. The oxyntic mucosa is rich in histamine, but the cellular storage sites differ from one species to another [5]. In some species, the main storage site is mast cells (for example dog and man), whereas in other species the main storage site is ECL cells (rat and mouse). The ECL cells are under both functional and trophic control of gastrin, and their possible role, and that of histamine, in the functional control of the parietal cells has attracted much attention [10]. The acute response to gastrin involves release of histamine and activation of histidine decarboxylase (HDC)^d [11-13]. Long-term stimulation with gastrin is known to cause growth of the oxyntic mucosa and hyperplasia of the ECL cells [14-17]. We will here discuss current knowledge of the physiological role of ECL-cell histamine.

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^d *Abbreviations:* HDC, histidine decarboxylase; α -FMH, α -fluoromethylhistidine.

INHIBITION OF HISTAMINE SYNTHESIS

Histamine is produced by the decarboxylation of L-histidine. This amino acid is the only one containing an imidazole ring. Animals do not synthesize this ring structure, which must be supplied from other organisms, i.e., bacteria and plants [18]. Decarboxylation of histidine is thought to be the chief source of histamine in all mammals [19]. The enzyme HDC catalyzes this reaction. The non-specific aromatic amino acid decarboxylase is also capable of decarboxylating histidine; however, HDC is quantitatively much more important [20, 21]. HDC is present in the oxyntic mucosa and has been localized to the ECL cells of the rat stomach [22]. The HDC activity of the oxyntic mucosa is high in species where the ECL cells constitute the predominant histamine-containing cell population. On the other hand, in species in which the oxyntic mucosa contains large numbers of mast cells and few ECL cells, the HDC activity has either been hard to detect or can be measured at very low levels only [23-25]. Interestingly, an inverse relationship between the histamine-forming capacity of the gastric mucosa and the sensitivity of parietal cells to exogenous histamine has been found when comparing different species [21].

One way of studying the role of ECL-cell histamine would be to inhibit the histamine-forming enzyme HDC and, thereby, deplete histamine from the tissue. This can be accomplished with α -fluoromethylhistidine (α -FMH), which is an inhibitor of this enzyme. α -FMH is a so-called suicide substrate, and its mechanism of action has been studied in detail [26-29]. The inhibition of α -FMH is irreversible in the sense that dialysis of the enzyme α -FMH complex does not restore enzyme activity. Available data indicate that α -FMH is an enzyme-activated and highly specific inhibitor [30]. *In vivo*, α -FMH has been found to be a specific inhibitor of HDC, but total inhibition of HDC activity has been difficult to achieve [28, 31, 32]. In most tissues, except brain and stomach, the histamine

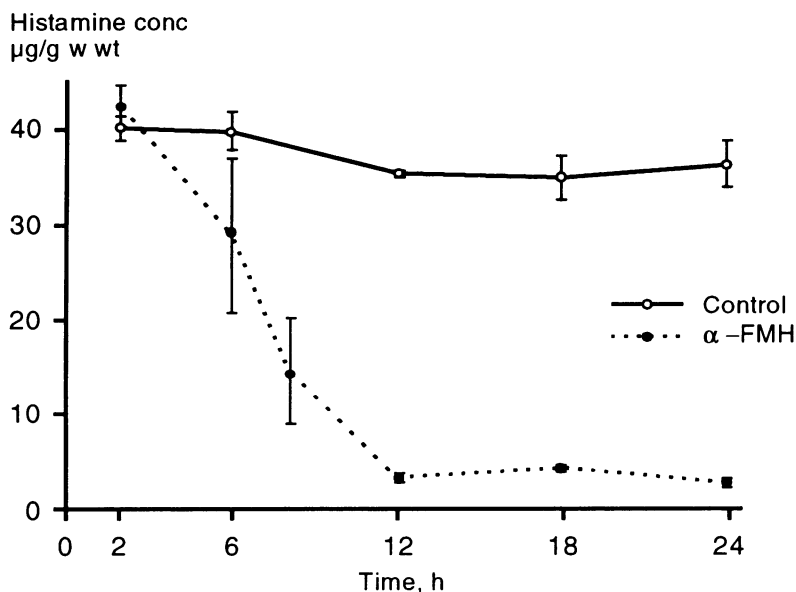


Figure 1. Rats treated with α -FMH (30 mg/kg.hr) by i.v. (2,6,8 hr) or s.c. (12,18,24 hr) infusion for up to 24 hr. Histamine concentrations were determined in oxyntic mucosal homogenate. Mean \pm SEM, n = 4-6.

content did not decrease appreciably after a single injection of α -FMH [28, 32]. In our early work with α -FMH, we treated rats orally twice daily for up to eight days and observed a reduction of the concentration of oxyntic mucosal histamine by 70 to 75 percent [33]. However, with twice daily dosing, the activity of HDC was not maximally inhibited over the 24-hour period. Instead, we started to use continuous infusion of α -FMH via osmotic minipumps to obtain a constant level of inhibition. Figure 1 shows how fast histamine disappeared from the oxyntic mucosa over a time span of 24 hours. After 12 hours infusion of the inhibitor maximal decrease was reached (80 to 85 percent). Despite prolonged infusion for up to six weeks, there was no further decrease in oxyntic histamine. Immunocytochemistry using histamine antibody revealed a virtual lack of histamine immunostaining in the ECL cells following α -FMH. On the other hand, histamine in the mast cells appeared unaffected [34]. From these data, we conclude that ECL-cell histamine represents at least 80 percent of the total histamine in rat oxyntic mucosa.

ECL-CELL HISTAMINE AND GASTRIC ACID SECRETION

The finding that H_2 -receptor antagonists inhibit not only histamine-stimulated but also gastrin- and vagus-stimulated acid secretion suggests that endogenous histamine plays a central role in the gastric acid secretory response [35, 36]. There are two prevailing hypotheses that attempt to define how histamine regulates the activity of the parietal cells (for recent reviews, see [10, 35-39]). In brief, the transmission hypothesis argues that histamine is the final mediator of acid secretion and that both gastrin and vagal excitation stimulate the release of histamine, leading to acid secretion. In a series of studies, Waldum et al. [40] have shown that gastrin is capable of releasing histamine from the isolated, perfused rat stomach in quantities that are sufficient to stimulate the parietal cells. The alternative hypothesis (i.e., the permission hypothesis) maintains that histamine acts as an amplifier of the direct actions of gastrin and acetylcholine on the parietal cells [41, 42]. Regardless of the model, it is important to identify the physiologically relevant local source of histamine. In rodents, most of the histamine is associated with the ECL cells, which readily release histamine in response to gastrin. In most of the larger mammals, the oxyntic mucosal histamine resides mainly in mast cells [5]. However, the gastric mast cells do not respond to gastrin [43]. Thus, although in the larger mammals the ECL cells contain a minor portion of the total gastric histamine, they may still represent the physiologically relevant source of histamine for acid secretion, provided that they respond to stimuli in the same manner as the ECL cells in the rat stomach [44, 45].

To study the role of ECL-cell histamine in the regulation of gastric acid secretion, we treated chronic gastric fistula rats with α -FMH by continuous subcutaneous infusion via osmotic minipump for two to six days [46], which resulted in an 85 percent reduction of the oxyntic mucosal histamine concentration. Acid-output was measured in these rats before and after stimulation with histamine, gastrin and insulin. We have no evidence that α -FMH directly impaired parietal cell activity [46].

Basal acid secretion was reduced by approximately 60 percent in α -FMH-treated rats compared to vehicle-treated rats, suggesting an involvement of ECL-cell histamine in basal acid secretion. However the H_2 antagonist ranitidine inhibited basal acid secretion by about 85 percent. The residual acid secretion after α -FMH treatment could reflect either an incomplete depletion of ECL-cell histamine or the contribution of histamine from another source than ECL cells. Pirenzepine, an M_1 antagonist, inhibited basal acid secretion by about 85 percent, indicating that an intact cholinergic pathway is necessary for a full basal acid response.

Histamine stimulated acid secretion in the gastric fistula rat. The response to histamine was not affected by pretreatment with α -FMH but prevented by ranitidine (Figure 2). The latter effect was independent of the mucosal histamine concentration. Gastrin stimulated acid secretion to a somewhat higher level than that reached after histamine stimulation. Pretreatment with either α -FMH or ranitidine prevented the stimulatory effect of gastrin (Figure 3). However, insulin stimulated acid secretion to the same level in both vehicle- and α -FMH-treated rats (Figure 4). Both ranitidine and pirenzepine prevented the response to insulin. In addition, we observed that ranitidine and pirenzepine, but not α -FMH, inhibited the acid secretion induced by pylorus ligation, which causes vagal stimulation [46, 47].

Depletion of ECL-cell histamine resulted in a near total loss of the acid response to gastrin. The minute response that remained could be due to the release of the small amounts of histamine that remained in the ECL cells. Alternatively, some other histamine source might be responsible. Whatever the explanation, it is clear that gastrin depends on ECL-cell histamine to exert its effect on the parietal cells. These data are in agreement with other studies in rat and dog, showing that infusion of gastrin produces a dose-dependent increase in histamine release [44, 48]. The response to vagal stimulation was not affected by depletion of ECL-cell histamine, an observation that is supported by a recent study in dogs in which pentagastrin infusion stimulated histamine release as well as acid secretion, whereas methacholine infusion stimulated acid output only [49]. In isolated parietal cells from several different species, cholinergic agents clearly stimulate aminopyrine accumulation whereas gastrin has a weak effect only, favoring the view that histamine plays a role in producing the full acid secretory response to gastrin [41, 50-54].

The M_1 antagonist pirenzepine was able to inhibit acid secretion stimulated by both insulin and pylorus ligation despite the fact that the muscarinic receptor on the parietal cell

Histamine-stimulated secretion

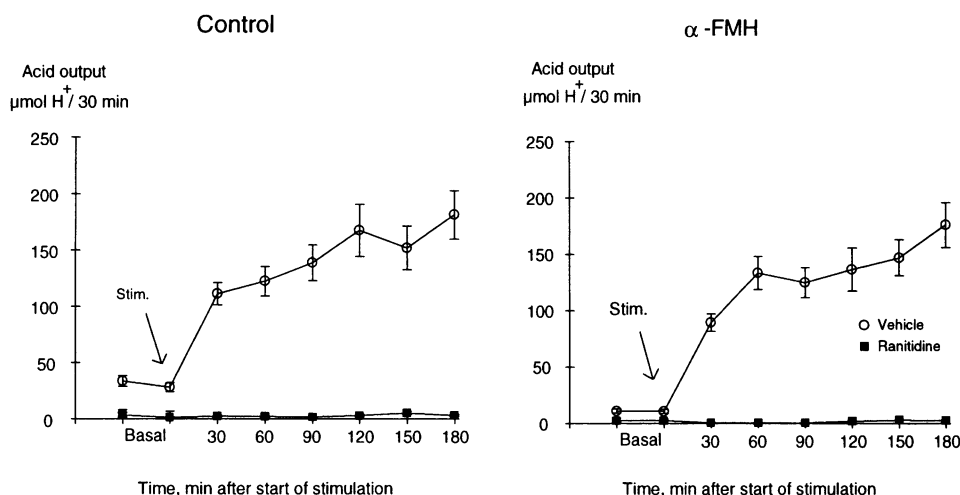


Figure 2. Histamine-stimulated gastric acid secretion in chronic fistula rats pretreated with vehicle (left) or α -FMH 3 mg/kg,hr (right) for at least two days. Histamine was given during the experiment (55 mol/kg,h given s.c.). Ranitidine was given 2 hr before the experiment (800 mol/kg given p.o.) and during the experiment (50 mol/kg,hr given s.c.). Mean \pm SEM, n = 10-12.

Gastrin-stimulated secretion

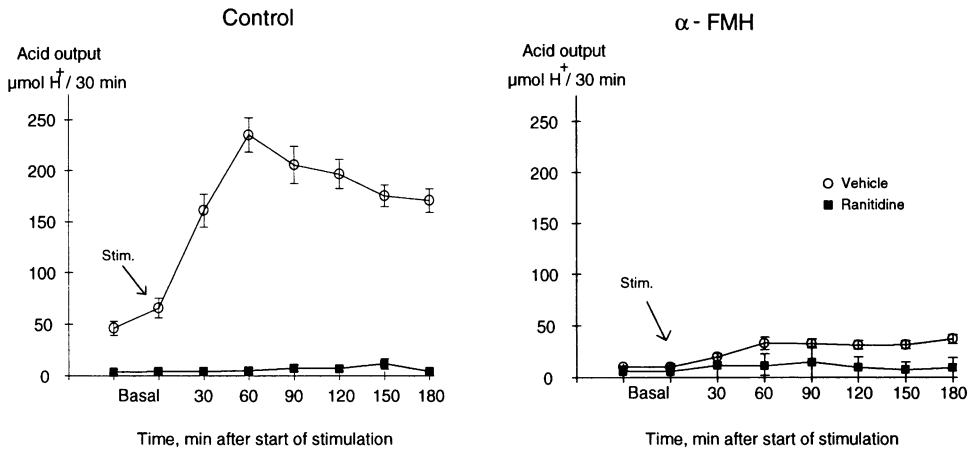


Figure 3. Gastrin-17-stimulated gastric acid secretion in chronic fistula rats pretreated with vehicle (left) or α -FMH 3 mg/kg,h (right) for at least two days. Gastrin-17 was given during the experiment (5 nmol/kg,hr given s.c.) Ranitidine was given 2 hr before the experiment (800 mol/kg given p.o.) and during the experiment (50 mol/kg,hr given s.c.). Mean \pm SEM, n = 8-12.

Insulin-stimulated secretion

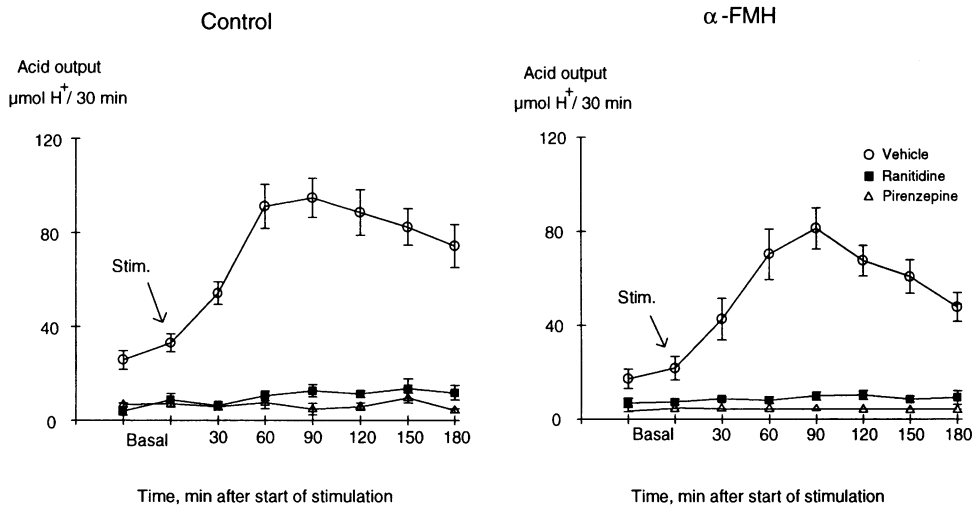


Figure 4. Insulin-stimulated gastric acid secretion in chronic fistula rats pretreated with vehicle (left) or α -FMH 3 mg/kg,h (right) for at least two days. Insulin was given as a bolus injection (0.6 IU/kg given s.c.). Ranitidine was given 2 hr before the experiment (800 mol/kg given p.o.) and during the experiment (50 mol/kg,hr given s.c.). Pirenzepine was given during the experiment (1 mg/kg,h given s.c.). Mean \pm SEM, n = 8-18.

is of the M_3 subtype [55]. This finding is in line with previous observations indicating that M_1 receptors, probably associated with neurons in intramural ganglia, are physiologically important in the regulation of acid secretion [56, 57]. The inhibitory effect of ranitidine on gastrin- or vagally-stimulated acid secretion in α -FMH-treated rats could reflect small amounts of histamine remaining in the ECL cells or it could reflect the contribution of histamine from another source (mast cells?).

Gastrin is able to stimulate aminopyrine accumulation in parietal cells isolated from pig and dog, but not from rat [41, 58]. This seems to correlate with the basal level of cAMP in the parietal cells of these different species, which is low in the rat compared with pig and dog [58-61]. In isolated pig parietal cells, pentagastrin induces a dose-dependent increase in aminopyrine accumulation, which could not be inhibited by an H_2 antagonist [62]. The effect of pentagastrin was reduced by inhibition of protein kinase A, showing a dependence of the cAMP level for the response to pentagastrin. Gastrin induces an increase in the intracellular Ca^{2+} levels in both ECL cells and parietal cells from rats but the effect on the parietal cell was blocked by an H_2 antagonist [63]. However, by adding DBcAMP in addition to the H_2 antagonist the response of the parietal cells to gastrin was restored. These results suggest that the gastrin response of the parietal cell depends upon the level of cAMP and that an elevation of intracellular cAMP plays a permissive role in the action of gastrin on the parietal cell [62, 63]. It has also been shown that carbachol is dependent on the cAMP level to be effective in stimulating aminopyrine accumulation, but the level of cAMP required may be lower for carbachol than for gastrin [58].

If we try to translate these *in vitro* data to the *in vivo* situation in our experiments, the depletion of ECL cell histamine would result in a lowering of the amount of local histamine available to stimulate the parietal cells. This could result in a decrease in the cAMP level in the parietal cells. Nonetheless, the cAMP level would still be enough for vagal stimulation to elicit the same response as in control rats. Adding an H_2 antagonist would prevent the remaining histamine from binding to its receptor on the parietal cell and would, thereby, lower the cAMP concentration to a level where vagal stimulation no longer could induce acid secretion. In the rat, ECL cell histamine would then be crucial for gastrin to exercise its acid-stimulating effect. Vagal stimulation might require smaller amounts of histamine to attain a cAMP concentration high enough to generate acid secretion. Alternatively, vagal stimulation is capable of releasing histamine from mucosal mast cells, resulting in acid production. It may be noted that mast cells are frequently found to be associated with nerve terminals also in the digestive tract and that acetylcholine causes release of histamine from mast cells [64].

ECL-CELL HISTAMINE AND ECL-CELL PROLIFERATION

Besides its action as a stimulant of gastric acid secretion, gastrin has a trophic effect on the oxyntic mucosa [14-17]. The clinical significance of the trophic action of gastrin has been obvious for many years, for example, the gastric mucosal hyperplasia coincident with Zollinger-Ellison syndrome and the mucosal atrophy observed following removal of the gastric antrum [65, 66]. There has been some controversy over the years regarding the question of whether gastrin has a trophic effect on tissues other than the oxyntic mucosa, i.e., the small and large intestine and the pancreas. By using repeated injections of pentagastrin Johnson and co-workers have shown trophic effects on the intestines and in the pancreas [67, 68]. However experiments using exogenous gastrin-17 or manipulation of the circulating endogenous gastrin levels have not confirmed these results [69-71]. Gastrin releases ECL-cell histamine, and it has been suggested that the released histamine mediates the trophic effect of gastrin [72, 73]. Histamine has been found to influence the mitotic rate

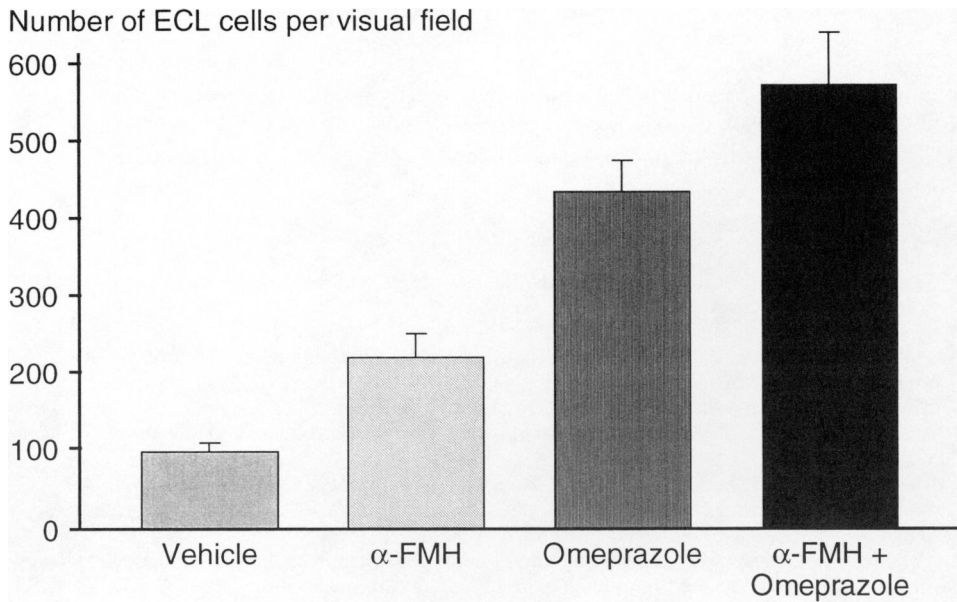


Figure 5. ECL-cell density after six weeks administration of vehicle, α -FMH (3 mg/kg,hr given s.c.), omeprazole (400 mol/kg given p.o.) or the combination of α -FMH + omeprazole. The cells were visualized by immunofluorescence using antibodies against HDC. Mean \pm SEM, n = 7-9.

of cells in the stomach and intestine of experimental animals [74, 75]. Recently it was argued that terfenadine, an H_1 -antagonist, inhibited ECL-cell proliferation induced by hypergastrinemia [76]. There are also reports favoring the existence of an H_3 receptor on the ECL cell modulating the gastrin-stimulated histamine secretion [77]. In other studies, exogenous histamine has not been found to mimic the trophic action of gastrin [78, 79]. We examined the possible involvement of ECL-cell histamine in the trophic response to long-term hypergastrinemia in rats [80]. Rats were treated with a high dose of omeprazole and/or α -FMH for six weeks. We found that treatment with α -FMH induced an increase in the plasma gastrin level, which was stable during the treatment period. Both the histamine concentration and the HDC activity in the oxyntic mucosa were reduced by approximately 80 percent compared to control rats. α -FMH alone increased the ECL cell number approximately two-fold. Omeprazole treatment resulted in sustained hypergastrinemia regardless of whether or not they received α -FMH. The hypergastrinemia resulted in an increase in stomach and mucosal weight as well as in mucosal thickness. Omeprazole alone raised the oxyntic mucosal histamine concentration and HDC activity while a combination of omeprazole and α -FMH reduced the histamine concentration and HDC activity to the same level as α -FMH only. The number of ECL cells was much increased in both groups and the ECL cells were found notably higher up in the glands, although they still predominated in the basal part (Figure 5). There were no statistically significant differences between rats treated with omeprazole or omeprazole plus α -FMH. We conclude, therefore, that the trophic response to gastrin occurs independently of ECL-cell histamine.

CONCLUSIONS

Gastrin stimulates acid secretion via the release of ECL-cell histamine. Although vagally induced acid secretion does not depend on ECL-cell histamine, it depends on a histaminergic pathway. Gastrin-evoked trophic effects in the oxyntic mucosa (including ECL cell hypertrophy/hyperplasia) occurs independently of ECL-cell histamine.

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